Exercise-induced bronchoconstriction (EIB) is the term used to describe the transient narrowing of the lower airways that follows vigorous exercise. Although EIB most commonly occurs in individuals with clinically recognized asthma, this condition is also reported in school children, armed forces recruits and elite athletes without asthma. Patients typically present with respiratory symptoms that are related to vigorous exercise. However, symptoms are poor predictors of EIB and should not be relied on for diagnosis. For example, EIB was demonstrated in children whose asthma appeared to be well-controlled on the basis of a questionnaire on symptoms.

Exercise-induced bronchoconstriction is identified by documenting a postexercise decrease in forced expiratory volume in 1 second (FEV₁) of 10% to 15% of the preexercise value. The forced expiratory volume in a half-second (FEV₀.₅) is useful for identifying EIB in young children aged 3 to 6 years old. The FEV₁ value may start to fall during exercise, but the lowest value is usually measured 5 to 12 minutes after the end of exercise. The decrease in FEV₁, if severe, is associated with a reduction in oxygen saturation and with hyperinflation of the lungs.

Spontaneous recovery of FEV₁ occurs within 30 to 60 minutes after an EIB episode. Some 50% of individuals become refractory to a repeated exercise stimulus within 4 hours.

**Epidemiologic Characteristics**

It is estimated that at least 80% of patients given a clinical diagnosis of asthma will have EIB at some stage of the disease process. Exercise-induced bronchoconstriction is among the first symptoms of asthma to appear, and it is typically the last symptom to disappear with treatment. Even after treatment with inhaled corticosteroids (ICSs), EIB can be demonstrated in a substantial proportion of patients with asthma.

Studies of EIB have been conducted with various cohorts in several countries. Surveys conducted 10 years apart (1993 and 2003) in Ghana showed an increase in prevalence of EIB in “urban rich” (4.2% to 8.3%), “urban poor” (1.4% to 3.0%), and rural (2.2% to 3.9%) children aged 9 to 16 years. In a study in Wales over a period of 30 years, the prevalence of EIB was reported to increase between 1973 and 1988 but decrease between 1988 and 2003 in the same geographical area. In a study of 802 school children in Australia, 157, or 19.6% of the children had EIB (defined as a decrease in FEV₁ ≥ 15%), and 40% of this group had no previous diagnosis of asthma.

Studies of athletes competing in the Olympic Games have provided useful data on asthma and EIB. There is a high prevalence of asthma among endurance Olympic athletes, both in winter sports (eg, cross-country skiing [17.6%], speed skating [16.2%]) and in summer sports (eg, cycling [15.3%], swimming [11.3%], modern pentathlon [10.1%]). Another sporting group for whom a diagnosis of EIB is important is scuba divers. Breathing dry air from a tank while swimming underwater or at the surface is a stimulus for EIB. In a laboratory analysis of 180 intending divers who had a history of asthma but no recent symptoms and who were currently taking no medications and were otherwise medically fit to dive, 17% had a 15% decrease in FEV₁ from baseline, in response to inhaling an aerosol of 4.5% saline. Results suggested that their asthma was currently active.

**Pathophysiologic Mechanisms**

The physiologic stimulus for EIB is the loss of water, by evaporation, from the airway surface while conditioning large volumes of air in a short time. This water loss can result in airway cooling and dehydration of the airway surface. When exercise is performed with the inhalation of hot humid air, there is a marked reduction or complete inhibition of EIB. There are two hypotheses as to how water loss causes the airways to narrow—the thermal hypothesis and the osmotic hypothesis.

According to the thermal hypothesis, EIB is a vascular event involving vasoconstriction resulting from airway cooling during exercise, followed by a reactive hyperemia when the airways rewarm on stopping exercise. This hypothesis does not implicate either bronchial smooth muscle or release of mediators in the mechanisms of EIB.

According to the osmotic hypothesis, an increase in osmolarity of the
Airway Injury

A recent hypothesis proposes that airway injury plays an important role in the development of EIB and bronchial hyperresponsiveness in elite athletes. According to this hypothesis, as the smaller airways are recruited into the air conditioning process, there is an increased risk of dehydration injury to the airway epithelium. Plasma exudation occurs during restoration of the epithelium. It is proposed that as the airway smooth muscle becomes repeatedly exposed to plasma-derived products, the contractile properties of the muscle change, rendering it more sensitive. This process may result in hyperresponsiveness to such agents as methacholine1 or it may result in EIB (Figure 1).30

Mediator Release

The mediators of EIB include prostaglandin D$_2$ (PGD$_2$), leukotrienes, and histamine. Histamine and PGD$_2$ are important in determining the severity of the decrease in FEV$_1$, and leukotrienes are important in sustaining this decrease. Indirect evidence supporting the role of these mediators includes the modifying effects of specific antagonists and cyclooxygenase inhibitors on EIB. Direct evidence implicating these mediators comes from studies reporting an increase in concentration in arterial plasma, induced sputum, and urine following exercise.40

There is an increase in urinary excretion of the major metabolite of PGD$_2$ and the cysteinyl leukotriene LTC$_4$ after hyperventilation. An increase in concentration of histamine, tryptase, and cysteinyl leukotrienes in sputum and an increase in histamine in arterial plasma have also been reported after exercise.1,40

Surrogates of Exercise

The variables affecting response to exercise may have led to the use of surrogates of exercise to identify EIB.45 The eucapnic voluntary hyperpnea (EVH) test is one such surrogate of exercise. The EVH test was developed and standardized in the 1980s to assess forced expiratory volume in 1 second for individuals with asthma and in healthy individuals. The test requires inhaling a dry gas mixture containing 4.9% to 5.0% carbon dioxide, 21% oxygen, and balance nitrogen.46 The protocol requires hyperventilation of the dry gas mixture for 6 minutes at 30 times FEV$_1$. The test is based on the principle that for most individuals, the maximum level of ventilation achieved during exercise is 17 to 21 times FEV$_1$—well below the ventilation achieved by voluntarily hyperventilating (ie, about 30 times FEV$_1$). Thus, the high ventilation rate and the dry air result in a low rate of false negative test results for EIB.
dom demonstrated that the EVH test could identify EIB in previously undiagnosed elite athletes. Further, for many athletes the clinical diagnosis of EIB was not confirmed by the test result. 47

Some disadvantages exist in performing exercise and EVH evaluations with dry air. Breathing dry air at high flow volume can give some individuals a sore throat. At high flow, the resistance of the breathing circuit must be very low if patients are to easily achieve their maximum ventilation. Finally, both the exercise and EVH tests use a maximum bolus stimulus and, as such, severe decreases in FEV₁ (>30% from baseline) often occur.

**Mannitol Dry Powder Challenge**

In order to avoid excessive declines in FEV₁, a test with mannitol can be used to identify the potential for EIB that is provoked by an increase in airway osmolarity and mediator release. The mannitol dry powder challenge requires the participant to inhale increasing doses of a dry powder of mannitol to a cumulative dose of 635 mg, with FEV₁ measured 60 seconds after each dose. 49,50 The mannitol test kit includes prepacked capsules and an inhaler device (Aridol; Pharmaxis Inc, Exton, Pennsylvania). A positive response to mannitol is indicated by a 15% decrease in FEV₁, a value that represents the 95% confidence interval observed in healthy individuals without

Figure 1. Flow chart describing the pathophysiologic events leading to exercise-induced bronchoconstriction (EIB) in a classic case of a patient with asthma (left) and the pathophysiologic events leading to the development of bronchial hyperresponsiveness and EIB in an athlete (right). Abbreviations: AHR, airway hyperreactivity; Ca, calcium; Cl, chlorine; FEV₁, forced expiratory volume in 1 second; K, potassium; Na, sodium; PGE₂, prostaglandin E₂. Reproduced with permission from Anderson and Kippelen. 30

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Prevention of EIB can be achieved on a short-term basis in the majority of patients with use of an inhaled β2-agonist (IBA), either short-acting or long-acting, immediately before exercise. 

The IBA inhibits EIB by stimulating the β2 receptors, leading to a reduced number of receptors on the mast cell surface so that mediator release is no longer inhibited after a few hours. 

The use of IBAs does not address the underlying inflammation that leads to EIB, and there are a number of limitations in relying solely on these drugs. For example, daily use of any IBA leads to tolerance to its benefits, both at the mast cell and the bronchial smooth muscle. This tolerance has a rapid onset, usually within 1 week, and is unaffected by concomitant use of ICS. Tolerance can manifest itself in several ways. First, a reduction in the duration of protection can occur, such that a short-acting IBA may protect for only 2 hours against EIB, and a long-acting IBA may protect for only 4 to 6 hours. Second, after an attack of asthma provoked by exercise, the time to recover to baseline FEV1 is prolonged. In addition, the IBA dose required for rescue is higher in patients taking IBAs on a daily basis. Finally, EIB has been reported as being more severe after introduction of an IBA on a daily basis. Tolerance in EIB likely results from down-regulation of the β2 receptors, leading to a reduced number of receptors on the mast cell surface so that mediator release is no longer inhibited after a few hours.
Drug tolerance (ie, tachyphylaxis) is acknowledged in the clinical setting in that patients with asthma who use IBAs daily are usually advised by their physicians to take additional inhalations of their medication immediately before exercise. Although these additional doses can overcome the tolerance problem in the short term, they contribute to sustaining the state of tolerance. Importantly, tolerance does not develop with irregular, intermittent use of IBAs (eg, 3 times a week). Full response to IBAs is usually restored after 72 hours of abstinence.

There are other medications that can be effectively used to inhibit EIB, but they do not usually prevent EIB completely. These agents include leukotriene antagonists and 5-lipoxygenase inhibitors. The most commonly reported agent used to treat patients with EIB is montelukast, which is taken as a tablet and requires several hours before it becomes effective. An advantage of montelukast over IBAs (eg, salmeterol) is that tolerance to the protective effect does not occur with daily use, and the duration of protection remains as long as 24 hours (Figure 2). Furthermore, montelukast enhances recovery of FEV₁ to baseline levels and reduces both the severity and length of the asthma attack after exercise. However, montelukast typically provides only about 60% protection against EIB—and not all users benefit to that extent.

Inconsistent findings have been reported with use of histamine antagonists. However, the combination of a histamine and a leukotriene antagonist has been found to inhibit the severity of the decrease in FEV₁ and the time of the asthma attack after exercise.

The mast cell stabilizing agents sodium cromoglycate and nedocromil sodium also inhibit EIB. The duration of the protective effects of these 2 medications against EIB is usually less than 3 hours. However, these agents have an immediate onset of action (allowing them to be inhaled just before the start of exercise), tolerance does not develop to these agents, and they do not need to be taken regularly. Their primary mode of action appears to be prevention of the release of PGD₂ and reduction of the release of leukotrienes.

There are nonpharmacologic methods of inhibiting or preventing EIB. For example, the 80% or more protection against EIB afforded by inspiring air conditioned to body temperature and fully saturated with water is greater than or equivalent to that provided by most medications in recommended doses. This method is not recommended as treatment, however, because the airways are a major means of reducing heat stress and maintaining normal body temperature. Nevertheless, this observation indicates that the EIB stimulus is close to the airway surface, emphasizing the importance of climatic conditions in determining EIB severity.

Some devices (eg, masks and heat exchangers) permit a small amount of water vapor to be rebreathed during exercise. This small amount of water may be effective in preventing some cases of EIB, because it reduces the number of airway generations required to condition the inspired air.

An unusual but practical way of preventing EIB is to determine if the patient becomes refractory to repeated exercise. Many years ago—before the advent of effective medications—some athletes found that they could provoke their EIB and then recover before the game, allowing them to complete the

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**Figure 3. Maximum decreases in forced expiratory volume in 1 second (FEV₁) after exercise by dose of the inhaled corticosteroid ciclesonide, at baseline, visit 1 (week 1), visit 2 (week 2), and visit 3 (week 3). Rate of improvement in the low-dose groups (40 µg, 80 µg) plateaued after 1 week of treatment, while this rate continuing to improve through week 3 in the high-dose groups (160 µg, 320 µg). Asterisk represents P<.05. Error bars denote the standard error of the mean.**

Adapted from Journal of Allergy and Clinical Immunology, 117(5), Subbarao P, Duong M, Adelroth E, et al. Effect of ciclesonide dose and duration of therapy on exercise-induced bronchoconstriction in patients with asthma, 1008-1013, 2006, with permission from Elsevier.

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**Table 3. Maximum decreases in forced expiratory volume in 1 second (FEV₁) after exercise by dose of the inhaled corticosteroid ciclesonide, at baseline, visit 1 (week 1), visit 2 (week 2), and visit 3 (week 3). Rate of improvement in the low-dose groups (40 µg, 80 µg) plateaued after 1 week of treatment, while this rate continuing to improve through week 3 in the high-dose groups (160 µg, 320 µg). Asterisk represents P<.05. Error bars denote the standard error of the mean.**

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game free of EIB. The reason for this effect is not well understood, though recent evidence suggests that tolerance develops to the contractile effects of the mediators released in the initial bout of exercise.75

Treatment
When EIB occurs, it responds rapidly to treatment with IBAs.76 For the long-term resolution of EIB in both children and adults, treatment with ICSs is required. Inhaled corticosteroids such as budesonide, ciclesonide, and fluticasone have all been shown to reduce severity of EIB within 3 to 12 weeks.16,17,77-79 The onset of protection achieved with ICSs is more rapid when higher doses are used (Figure 3).78

The value of regular treatment with an ICS alone is that the majority of patients with EIB have normal spirometry values requiring a bronchodilator only before exercise. In patients with suboptimal spirometry values, combination of a long-acting IBA with an ICS has been shown to reduce severity of EIB.16,17 In a pilot study, however, withdrawal from the long-acting IBA while remaining on the ICS demonstrated a reduction in the severity of EIB in children.80

Because ICSs are so effective in long-term treatment of EIB, patients should verify, on a regular basis, whether they still have EIB and still need to take an IBA immediately before exercise. Such verification will help ensure that patients are not taking extra doses of IBAs unnecessarily.

Some dietary products, including fish oil, have been reported to provide protection against EIB.81,82 It is important to note that the severity of EIB in such studies was mild, and individuals with moderate to severe EIB cannot rely solely on diet to prevent attacks.

Finally, physical fitness plays a role in EIB occurrence. In individuals who are unfit, EIB will occur at a lower intensity of exercise. Some studies have examined improving physical fitness as a way of treating patients with EIB.83,84

Final Notes
In summary, exercise-induced bronchoconstriction occurs in people with clinically recognized asthma and in elite athletes without other signs of asthma. EIB is a consequence of the thermal and osmotic effects of evaporative water loss in conditioning large volumes of air over a short period. Exercise testing is difficult to standardize and responses vary considerably over days. For this reason, surrogates of exercise such as eucapnic voluntary hyperventilation and dry powder mannitol, given by inhalation, are often used to identify potential for EIB. Mast cell mediators (eg prostaglandins, leukotrienes and histamine) and neuropeptides from sensory nerves are all likely to contribute to EIB. Exercise-induced bronchoconstriction is prevented in the short-term by inhaling a β2 agonist immediately before exercise, and in the long-term by regular treatment with inhaled corticosteroids.

There are no pharmacologic approaches to treating patients with EIB that include using face masks in cold weather and improving the physical fitness of those who are unfit.

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